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Effect of Chronic Alcohol Ingestion on Bone Mineral Density in Males without Liver Cirrhosis

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Background : Osteoporosis in men is an important public health problem. Because of the tendency of the numbers of the elderly population to increase, and age-specific incidence of fractures, it is inevitable that the health burden due to fractures will increase. Chronic alcoholism is associated with other risk factors, such as poor nutrition, leanness, liver disease, malabsorption, vitamin D deficiency, hypogonadism, hemosiderosis, parathyroid dysfunction and tobacco use, and these may contribute to the pathogenesis of bone disease related to alcoholism. Chronic alcohol intake may reduce bone density, but can also increase bone density. It is well established that liver disease also induces bone density changes, thus it is difficult to distinguish the role of liver disease from that of alcohol itself in the bone alterations occurring in patients with chronic alcohol consumption. Chronic male alcoholics, not having liver cirrhosis were studied to assess the effect of chronic alcohol consumption on their bone mineral density.

Methods : The study subjects comprised of 18 chronic heavy drinkers of more than 40 g of alcohol per day for at least 3 years and 18 age-matched controls who drank less than 20 g of alcohol per day. The serum and urinary parameters of bone and mineral metabolism were determined. The bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry at four axial sites (lumbar spine, femoral neck, Ward's triangle and trochanter).

Results : The alcoholic and control patients drank an average of 97.6 g and 7.2 g of alcohol per day. Osteocalcin, a marker of bone formation, was slightly decreased in alcoholic patients, and deoxypyridinoline, a marker of bone resorption, was slightly increased, but the difference was not statistically significant ($p>0.05$).

There were no differences between the two groups in the levels of free testosterone, estradiol, 25(OH) vitamin D and parathyroid hormone. The Ward's triangle and trochanter BMDs of the femur were significantly lower in the alcoholics than the controls, and lumbar spine BMD was decreased in proportion to the total alcohol intake in the alcoholics ($r=-0.625$, $p=0.01$).

Conclusion : We suggest that chronic alcohol consumption induces low bone density in the femur Ward's triangle and trochanter. There was also a significant inverse correlation between the lumbar spine BMD and the total amount of alcohol consumed.

Large scaled randomized and prospective studies are needed to clarify the pathogenesis of alcohol-induced osteoporosis.

Key Words : Osteoporosis, Alcoholism, Bone Density

INTRODUCTION

Osteoporosis in women has recently been emphasized. However in 1990, about 30% of 1.66 million hip fractures worldwide occurred in men[1]. The rate of male hip fracture were same of that of female fracture from 1972 to 1984 in

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Canada[2]. In women, the pathophysiology, risk factors, etiology and treatment of osteoporosis have been well defined[3], but those for males remain to be fully elucidated.

Osteoporosis in men is quite different from that in women. In men, bone losses are gradual[3, 4]. Osteoporosis in men has been termed idiopathic (primary) osteoporosis if no known causes can be identified on clinical and laboratory grounds. Secondary osteoporosis is when the causes of osteoporosis are known. It has been suggested that the causes of secondary osteoporosis are hypogonadism, smoking, medications, such as steroids or anticonvulsants, alcohol abuse, gastrointestinal disorders, low body mass index (BMI), hyperparathyroidism, thyrotoxicosis and glucocorticoid excess. Secondary osteoporosis is meaningful in the proper treatment and prevention for bone loss reduction[4, 5].

Kim et al[6] reported on the clinical characteristics and causes of primary male osteoporosis in Korea, and found that low BMI (a mean BMI of 22.1 kg/m^2), low calcium intake, hypercalciuria, vitamin D deficiency, subclinical hypovitaminosis D, testosterone deficiency and low IGF-1 levels were the major factors.

The long-term consumption of alcohol has been established can reduce bone density and increase fracture rates in men. However, the effect of alcohol depends on the age at initiation, the total alcohol consumed and on the frequency and duration of consumption.

There have been conflicting reports suggesting that chronic and excessive alcohol intake might reduce bone density[7-9], and other that say it does not[10, 24]. Some reports have suggested that moderate alcohol consumption might increase bone density[11-14].

The influence of alcoholic liver cirrhosis on bone and mineral metabolism has been reasonably well defined, however the effect of alcohol itself on bone loss remains obscure.

The aims of the present study were to evaluate the alcohol-induced changes of bone and mineral metabolism, and reassess any possible link between alcohol abuse and bone mineral density in non-cirrhotic male alcoholics.

MATERIALS AND METHODS

1. Subjects

The subjects of this study were 18 males with an alcohol-drinking habit of more than 40 g of ethanol/day and 18 age matched controls who consumed less than 20 g of ethanol/day. All subjects were ambulatory patients seen at the Won-ju Christian Hospital between January 2000 and December 2000. The alcohol drinkers were all active drinkers and none had abstained at the time of the study. Eighteen healthy moderate alcohol drinkers had a daily alcohol intake history of less than 20 g ethanol/day. Subjects with an endocrine disease (diabetes mellitus, thyroid disease, Cushing's disease, etc.) were excluded from this study. Patients with bone and mineral diseases, as well as who had been taken steroids, anti-convulsants, vitamin D, heparin, calcium supplements, were also excluded.

2. Methods

(1) Medical and biochemical examination

All the subjects heights and weights were recorded and their adiposity checked by a bioelectrical method (Inbody 2.0, Biospace®). A dietitian asked about their daily calories, protein and calcium intake using a Food Questionnaire, and they were also asked about their smoking history and family history of osteoporosis. Measurements for liver enzymes (AST and ALT), serum protein, creatinine, calcium, phosphorus, hemoglobin, platelet count and prothrombin time were performed, and the 24 hour urinary calcium excretion analysed.

(2) Alcohol consumption habit examination

All subjects were asked about their drinking habits, kinds of alcohol, amounts of ethanol consumed per day, duration of alcohol consumption and age at initiation. The amounts of alcohol in each kind of drink were considered as follows: soju (distilled liquor) one hop (180 mL), 45g, makkolli (unstrained rice wine) one toe (1800 mL), 144g and beer 1 bottle (640 mL), 25.6 g. The cumulative alcohol intake was calculated as follows: grams of alcohol ingested per day×number of years of alcohol use.

(3) Diagnosis of alcoholic liver disease

Alcoholic liver disease was defined as follows: any elevated levels of AST, ALT, alkaline phosphatase or γ-GT. Moreover, the hepatitis B antigen and hepatitis C antibody were all negative, with no accompanying endocrine disorders, such as obesity, diabetes mellitus, thyroid disease, Cushing's disease, etc. Patients medicated with herbs or other drugs were excluded. Patients who had hepato-biliary diseases were also excluded. Patients with hypoalbuminemia, hyperglobulinemia, prolonged prothrombin time or decreased platelet count were also excluded as these are factors of suspected liver cirrhosis. Cases with an abnormal echo pattern in liver, or spleen enlargement detected by ultrasonogram, were regarded as suspected liver cirrhosis.

(4) Hormone study

① 25-(OH)-Vitamin D

The serum 25-(OH)-vitamin D was measured with a competitive RIA by 25-(OH)-VIT.D_3-RIA-CT (BioSource Europe

S.A, Belgium, Germany).

The intra-and inter-assays CV were 6.1 and 7.1%, with a sensitivity of 0.6 ng/mL.

② Intact PTH

The serum i-PTH was measured with a competitive RIA by I-PTH IRMA CT (RADIUM SpA-Via del Mare, Italy). The intra-and inter-assays CV were 1.9 and 2.6%, with a sensitivity of 12 pg/mL.

③ Estradiol

The serum estradiol was measured with a Coat-A-Count Estradiol ^{125}I RIA (DPC®, California, USA). The intra-and inter-assays CV were 4.0 and 4.2%, with a sensitivity of 8 pg/mL.

④ Free testosterone

The serum free testosterone was measured with a competitive RIA coated tube, using a DSL-4900 Active Free Testosterone Coated tube RIA (Diagnostic products, California, USA). The intra-and inter-assays CV were 5.5 and 10.9%, with a sensitivity of 0.18 pg/mL.

(5) Biochemical markers of bone turnover

① Osteocalcin

The serum osteocalcin was measured with a competitive RIA coated tube, by OSCA test Osteocalcin (BGP) (BRAHMS Diagnostica GmbH, Berlin, Germany).

The intra-and inter-assays CV were 2.4% and 5.6%, with a sensitivity of 1.8 ng/mL.

② Deoxypyridinoline (dpd)

The 24 hour urine deoxypyridinoline was measured by a competitive RIA, by Pyrilinks®-D (Metra Biosystems. Inc, California, USA).

The intra-and inter-assays CV were 4.3 and 3.1%, with a sensitivity of 1.1 nmol/L.

(6) Bone mineral density

The bone mineral density was measured by dual energy X-ray absorptiometry (DXA, LUNAR®) at four axial sites (lumbar spine, femur neck, Ward's triangle and trochanter). The CV in the lumbar spine and femur were both 1%.

Osteoporosis was considered if the bone mineral density was more 2.5 SD (standard deviation) below that of the young adult man value. Osteopenia was considered if the BMD lay between 1 and 2.5 SD below that of the young adult man value. Normal was considered if the BMD was no more than 1 SD below that of the young adult mean value.

3. Statistical analysis

All data are expressed as the mean SD. The SPSS 10.0 (Chicago, USA) programs were used for the statistical analyses. The differences between the groups were assessed by Chi-squared tests, and any correlations between the bone mineral density and total alcohol consumption were calculated by the Pearson correlation method. A significance level of 5% was chosen for all the tests (p value <0.05).

RESULTS

1. Clinical data and basic laboratory parameters

The mean ages in the drinker and control groups were 50 years, ranging from 30- to 82 years, and 51 years, ranging from 24- to 75 years, respectively. BMI of the drinkers was lower than that for the mean Korean male (23.5 kg/m^2), as reported in 1996 for Koreans. However, there was no significant difference between the drinker and control subjects. The mean muscle and fat masses were lowed in the drinkers than in the control subjects, but this was not statistically significant (Table 1).

Table 1. Clinical characteristics between alcoholics and controls

	Alcoholics (n=18)	Controls (n=18)	p value
Age (years)	50.2±9.5	51.2±14.0	NS
Height (cm)	165.8±5.9	164.6±7.8	NS
Weight (kg)	58.4±8.4	61.8±10.5	NS
BMI (kg/m^2)	21.0±3.0	22.7±2.8	NS
Muscle mass (kg)	45.0±7.2	47.7±7.4	NS
Fat mass (kg)	10.4±3.8	11.4±4.6	NS

Data express mean±SD.
NS, not significant.

2. Daily alcohol consumption calcium, protein intake and urinary calcium excretion

The drinkers drank an average of 97.7 g of alcohol/day, ranging from 43- to 430 g. Of the 18 controls, nine had no history of alcohol consumption and only one case drank as much as 20 g/day.

The kinds of alcohol were various; with 13 cases of soju, 4 of makkolli and one of beer. The mean duration of alcohol consumption was 22.3 years.

In the drinker group, the mean age of initiation was 22 years old, with 4 of the 18 drinkers having started before the age of 20 years.

The daily calcium intake was 639.8mg in the drinkers, compared 585.1 mg in the controls, but with no statistical significant. There was also no difference in the daily protein intake.

The mean levels of 24 hour urinary calcium excretion were 257.8 and 158.5 mg in the drinkers and controls, respectively,

but with no statistical significant (Table 2).

Table 2. Alcohol, calcium and protein intakes of the alcoholics and controls

	Alcoholics (n=18)	Controls (n=18)	*p* value
Alcohol intake (g/day)	97.7±90.7*	7.3±11.8	0.001
Alcohol intake duration (year)	23.8±13.8	-	
Daily calcium intake (mg/day)	639.8±207.8	585.1±242.7	NS
Daily protein intake (mg/day)	66.4±22.8	59.2±28.2	NS
Daily urine calcium (mg/day)	257.8±300.2	158.5±62.6	NS

Data express mean±SD.
*: p <0.05 between of alcoholic and controls.

3. Biochemical characteristics

The drinkers had higher serum AST, ALT, alkaline phosphorus and γ-GT levels than the control subjects, but there were no differences in the serum total protein, albumin, calcium or phosphorus between the two groups (Table 3).

Table 3. Values for basic blood and urine parameters between the alcoholics and the controls

	Alcoholics (n=18)	Control (n=18)	*p* value
Total protein (g/dL)	6.1±1.3	6.2±1.0	NS
Albumin (g/dL)	3.4±0.7	3.6±0.7	NS
AST (U/L)	230.4±406.2*	32.6±37.0	0.04
ALT (U/L)	78.5±102.7*	19.7±12.6	0.03
Total bilirubin (mg/dL)	1.3±1.0	1.4±2.6	NS
Alkaline phosphate (U/L)	108.6±41.2*	70.1±24.5	0.03
r-GT (U/L)	599.3±971.8*	26.9±15.8	0.03
Corrected Calcium (mg/dL)	8.1±1.9	8.1±0.6	NS
Phosphorous (mg/dL)	3.0±1.5	3.4±0.6	NS
Hemoglobin (g/dL)	11.2±2.2	12.8±2.2	NS
Platelet count (/mm^3)	267×10^3	246×10^3	NS
Prothrombin time (%)	95.5±16.1	97.0±25.7	NS

Data express mean±SD.
*: p < 0.05 between alcoholic and controls.

4. Parameters of bone and mineral metabolism

The mean serum osteocalcin concentration was lower in the drinker than in the control subjects (4.2 vs. 6.1 ng/mL).

The mean urinary dpd concentration was higher in the drinkers than the controls (18.4 vs. 13.7 nnmol/l), but there were no statistical differences in the osteocalcin and dpd between the two groups.

The mean serum 25-(OH)-vitamin D concentrations were 21.7 and 27.8 ng/mL in the drinker and control subjects, respectively, but this was statistically insignificant. 3 of the drinker and 2 of the control subjects were vitamin D deficient, which was defined as a serum 25-(OH)-vitamin D concentration lower than 12.0 ng/ml. The serum levels of intact parathyroid hormone, free testosterone and estradiol were similar in the drinkers to those in the controls (Table 4).

Table 4. Parameters and hormones related to bone and mineral metabolism in the alcoholics and the controls

	Alcoholics (n=18)	Controls (n=18)	*p* value
Osteocalcin (ng/mL)	4.2±2.6	6.1±4.2	NS
Deoxypyridinoline (nmol/L)	18.4±14.1	13.7±11.8	NS
25-(OH)-vit D (ng/mL)	21.7±9.4	27.8±11.0	NS
Intact PTH (pg/mL)	42.9±22.4	40.6±16.3	NS
Free testosterone (ng/mL)	12.0±5.0	11.9±4.5	NS
Estradiol (pg/mL)	18.4±14.1	13.7±11.8	NS

Data express mean±SD.

5. Bone mineral density measurements

The mineral density in the femoral wards and trochanter were significantly lower in the drinker than in the control subjects.

In the drinkers, there were 4 cases of osteoporosis, 9 of osteopenia, with 5 normal bone density cases. In the control subjects, there were 3 cases of osteoporosis, 2 of osteopenia and 13 with normal bone density (Table 5).

Table 5. Bone Mineral Density in alcoholics and controls.

BMD (g/cm^2)	Alcoholics (n=18)	Controls (n=18)	*p* value
L-Spine L2	1.005±0.14	1.124±0.21	NS
L3	1.057±0.16	1.135±0.25	NS
L4	1.048±0.17	1.128±0.24	NS
L2-3	1.032±0.14	1.130±0.22	NS
L2-4	1.040±0.14	1.131±0.22	NS
L3-4	1.053±0.15	0.908±0.15	NS
Femur Neck	0.844±0.12	0.908±0.15	NS
Wards	0.665±0.14*	0.773±0.17	0.04
Troch	0.732±0.11*	0.818±0.12	0.03

Data express mean±SD.
*: p<0.05 between the alcoholic and controls.
Wards, Ward's triangle; Troch, Trochanter.

6. Correlation between BMD and index of cumulative alcohol intake in drinkers

A significant inverse correlation in lumbar (L2-L4) spine was found between the BMD and the index of cumulative alcohol intake (Figure 1).

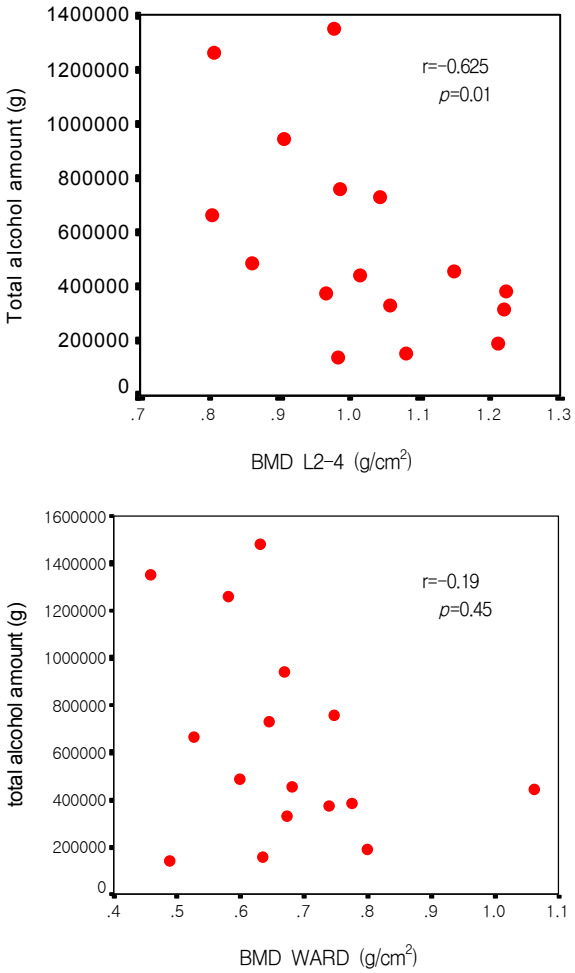

Figure 1. Correlation of total alcohol amount and L-spine & femur neck.

DISCUSSION

The present study has showns that subjects with chronic alcoholism, but with no evidence of liver cirrhosis, may have a reduce bone density, and that some relationship exists between the amount of alcohol consumed and the degree of bone loss.

In contrast with females, the pathophysiology of males relating to osteoporosis remains to be fully elucidated. Moreover, methods for the diagnosis of male osteoporosis have not been established. The WHO criteria for females have, until now, been used to diagnose male osteoporosis. If the age-adjust BMD (T score on DXA) is more than 2.5 SD below the mean value, suspicion of a secondary causes for osteoporosis should be heightened.

Hypogonadism, especially a reduced testosterone level, was an important factor in male osteoporosis. An adult male may have reduced serum testosterone concentrations of 1.2% per year. Estrogen in males is considered important hormone for maintaining bone mass[3, 15, 16]. In addition to estrogen, growth hormone (GH) and insulin like growth factor (IGF-1) have become known as important hormones for supporting bone mass[17].

In this study, the serum IGF-1 levels were not checked. However, reduced IGF-1 levels are a cause of male osteoporosis[17], and lower IGF-1 levels have been reported correlate with alcohol-induced osteoporosis[18]. Rojdmark et al[19] suggested that alcohol might inhibit the syntheses of IGF-1 and IGFBP (insulin like growth factor binding protein) in the liver.

The mechanism of ethanol associated bone mass loss is not understood, but there are likely to be several contributing factors. Ethanol reduces the bone mineral density due to the inhibition of bone formation[20-23]. Serum osteocalcin is a small peptide, synthesized by osteoblast, which is released into the circulatory system. At present, osteocalcin is regulated as the most sensitive and specific biochemical marker of osteoblast activity in normal subjects and in patients with metabolic bone disease. In this study, the serum osteocalcin levels were found to be lower in the drinkers, but with no statistical significant. By rechecking the osteocalcin levels after ethanol withdrawal, the indirect effects of ethanol on bone formation may be realized.

Pyridinoline (or hydroxylysyl pyridinoline: pyd), deoxy-pyridinoline (dpd) or lysyl pyridinoline (D-pyd) are known to be markers of bone resorption. The urinary dpd levels might be increased in alcoholics[23, 24, 31], and associated with significant increases in the osteoclast numbers[7]. In our study, the drinkers had higher dpd levels than the control subjects, presumably reflecting higher bone resorption rates, but this was not significant.

Impairment of vitamin D metabolism in chronic alcoholism may contribute to the development of osteoporosis associated with poor nutrition, malabsorption and alcoholic liver cirrhosis. Laitenen et al[24] reported that chronic alcohol abuse caused vitamin D metabolism abnormalities, which was not the case with acute alcohol intake. Chronic alcoholics usually have low serum levels of 25-hydroxyvitamin D[25(OH)D_3], 1,25$(OH)_2D_3$ and 24,25$(OH)_2D_3$, but not all studies support these findings, and many studies have revealed normal or increased levels of one or more of these metabolites[25]. Barre et al[25] suggested

a combination of factors, such as malabsorption, poor dietary intake, lack of sunlight exposure, or a direct effect of ethanol, might affect vitamin D metabolism. For the purpose of maintaining $1,25(OH)_2D$ levels in vivo, the serum 24(OH)D levels must be conserved at more than 20 ng/ml[26, 27]. However, 8 of the drinkers and 3 of the controls were vitamin D deficient in this study. In our study, the 24(OH)D levels could not be rechecked, which limited to our exact interpretation of the vitamin D levels, because they were affected by seasonal variations and nutrition stati.

In chronically alcohol intoxicated animals, the serum PTH levels have been found to be elevated, slightly elevated[22, 28, 29, 31] and decreased[30]. Bike et al[28] reported that alcohol intake at a young age might affect the PTH metabolism and bone metabolism, but chronic alcohol intake didn't. In our study, the alcohol drinkers had higher PTH levels, but this was not statistically significant.

Hypogonadism, due to the aging process, and secondary hypogonadism also reduces the bone mineral density in both men and women. The importance of estrogen for maintenance bone mass has become established in men as well as in women[15, 16, 32-34].

Alcohol may have a toxic effect on the testis, resulting in decrease serum testosterone levels and dysregulation of the hypothalamic-pituitary-gonadal axis. In our study, both the drinkers and the control subjects had lower free testosterone concentrations than the mean adult male testosterone concentration of 13-40 ng/mL.

The mean estradiol concentrations were no different between the groups. Therefore, this study has showns that the gonadal function was affected by alcohol intoxication, as well as liver disease itself.

Increased urinary calcium excretion was consistently found in the chronic alcohol drinkers. Hypercalciuria was affected by increased calcium absorption in the gut, urinary calcium over excretion or increasing bone resorption. In our study, the daily calcium intake and urinary calcium excretion were increased in the alcohol drinkers, but not significantly. To evaluated the alcohol induced changes in the bone and mineral metabolisms, bone density and bone mineral metabolism related parameters must be studied after alcohol withdrawal.

The bone mineral densities in the femoral ward triangle and trochanter were significantly lower in the drinkers than in the control subjects, but not in the lumbar spine. Shuhei et al[35] reported the bone density of femur was decreased more than in the lumbar spine after feeding ethanol to Wister rats for 6 weeks. The lumbar spine consists of 60~70% spongy bone, whereas the femur consists mostly of cortical bone. However, they insisted that no conclusion could be drawn as to whether the spongy or cortical bone was more strongly affected by the BMD-reducing effect of alcohol, as no longitudinal study had been conducted on the lumbar BMD. Alcohol abuse reduces bone density, but this reduction is not always reported. Laitinen et al[24] found no reduction in the bone density at the lumbar spine or proximal femur in 27 eugonadal non-cirrhotic alcoholic men. Holbrook et al[12] reported that increasing alcohol consumption was associated with higher bone densities, at the proximal femur in men, and the spine in women. The pathogenesis of increasing bone density with chronic alcohol consumption has not been established, but it may be estimated that alcohol promotes the production of adrenal androstenedion and increases the conversion to estrogen. So, increased estrogen may prevent bone loss in chronic alcoholics.

In this study, there was significant inverse correlation between the lumbar spine BMD and the cumulative amount of alcohol consumption, but this was not the case with the femur. In the femur, there were some cases of reduced bone density, regardless of the level of alcohol intake. So, there was no significant inverse correlation in the BMD in the femur with cumulative alcohol consumption.

An altered polyamine metabolism may explain the reason for the antiproliferative effect of ethanol on osteoblasts. Manolagas et al[36] reported that interleukin-1 (IL-1), IL-6 and IL-11, and tumor necrosis factor (TNF) can stimulate osteoclast development, thereby the bone resorption process. Histomorphometric studies must be performed to assess the direct effect of alcohol on bone cells. The mechanism for the production of alcohol-associated osteoporosis is unclear, but there appears to be a direct effect of alcohol on bone cells, with an indirect, or modulating, effect through mineral-regulating hormones, such as vitamin D metabolism, parathyroid hormone, and testosterone.

Chronic alcohol abuse might reduce the lumbar spine and femur densities, but was found to significantly reduce that of the femur. A significant inverse correlation in lumbar spine was found between the BMD and the index of cumulative alcohol intake. Therefore, chronic alcohol abuse might reduce the femur BMD, and thus increase the fracture rates. For the purpose of the exact pathogenesis of alcohol induced osteoporosis, large scaled randomized and prospective studies, combined with histomorphometric studies, will be needed.

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